**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 209/42, A61K 31/40, C07D 401/12 | A1

(11) International Publication Number: **WO 98/45262**

(43) International Publication Date: 15 October 1998 (15.10.98)

(21) International Application Number: PCT/EP98/02010

(22) International Filing Date: 7 April 1998 (07.04.98)

(30) Priority Data:
FI97A000072 8 April 1997 (08.04.97) IT

(71) Applicant *(for all designated States except US)*: MENARINI RICERCHE S.P.A. [IT/IT]; Via Tito Speri, 10, I–00040 Pomezia (IT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SISTO, Alessandro [IT/IT]; Via Proba Petronia, 43, I–00136 Rome (IT). FINCHAM, Christopher [GB/IT]; Viale Manzoni, 51, I–00040 Pomezia (IT). POTIER, Edoardo [IT/IT]; Piazza Federico II, 6, I–00040 Pomezia (IT). TERRACCIANO, Rosa [IT/IT]; Via della Tecnica, 76, I–00040 Pomezia (IT).

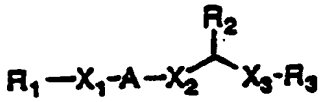
(74) Agent: GERVASI, Gemma; Notarbartolo & Gervasi S.p.A., Corso di Porta Vittoria, 9, I–20122 Milan (IT).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: PSEUDO–PEPTIDE COMPOUNDS AS ANTAGONISTS OF NEUROKININES

(57) Abstract



(I)

Compounds of general formula (I) where $R_1$ is (A) $X_1$ –CONH–, $X_2$ is –$NR_{12}CO$–, wherein $R_{12}$ is hydrogen or methyl; $X_3$ is chosen in the group consisting of –$NR_{12}CO$–, $NR_{12}CONH$–, where $R_{12}$ is as defined above; A is (B) where B, C, D, and E, independently from each other, may be CH or N, $R_2$ is chosen in the group consisting of (C) considering that when one of the variable B, C, D, E is N, the others are CH. The compounds of the present invention have shown an antagonist activity of the action of the P substance, neurokinin A, and neurokinin B.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **AL** | Albania | **ES** | Spain | **LS** | Lesotho | **SI** | Slovenia |
| **AM** | Armenia | **FI** | Finland | **LT** | Lithuania | **SK** | Slovakia |
| **AT** | Austria | **FR** | France | **LU** | Luxembourg | **SN** | Senegal |
| **AU** | Australia | **GA** | Gabon | **LV** | Latvia | **SZ** | Swaziland |
| **AZ** | Azerbaijan | **GB** | United Kingdom | **MC** | Monaco | **TD** | Chad |
| **BA** | Bosnia and Herzegovina | **GE** | Georgia | **MD** | Republic of Moldova | **TG** | Togo |
| **BB** | Barbados | **GH** | Ghana | **MG** | Madagascar | **TJ** | Tajikistan |
| **BE** | Belgium | **GN** | Guinea | **MK** | The former Yugoslav Republic of Macedonia | **TM** | Turkmenistan |
| **BF** | Burkina Faso | **GR** | Greece | | | **TR** | Turkey |
| **BG** | Bulgaria | **HU** | Hungary | **ML** | Mali | **TT** | Trinidad and Tobago |
| **BJ** | Benin | **IE** | Ireland | **MN** | Mongolia | **UA** | Ukraine |
| **BR** | Brazil | **IL** | Israel | **MR** | Mauritania | **UG** | Uganda |
| **BY** | Belarus | **IS** | Iceland | **MW** | Malawi | **US** | United States of America |
| **CA** | Canada | **IT** | Italy | **MX** | Mexico | **UZ** | Uzbekistan |
| **CF** | Central African Republic | **JP** | Japan | **NE** | Niger | **VN** | Viet Nam |
| **CG** | Congo | **KE** | Kenya | **NL** | Netherlands | **YU** | Yugoslavia |
| **CH** | Switzerland | **KG** | Kyrgyzstan | **NO** | Norway | **ZW** | Zimbabwe |
| **CI** | Côte d'Ivoire | **KP** | Democratic People's Republic of Korea | **NZ** | New Zealand | | |
| **CM** | Cameroon | | | **PL** | Poland | | |
| **CN** | China | **KR** | Republic of Korea | **PT** | Portugal | | |
| **CU** | Cuba | **KZ** | Kazakstan | **RO** | Romania | | |
| **CZ** | Czech Republic | **LC** | Saint Lucia | **RU** | Russian Federation | | |
| **DE** | Germany | **LI** | Liechtenstein | **SD** | Sudan | | |
| **DK** | Denmark | **LK** | Sri Lanka | **SE** | Sweden | | |
| **EE** | Estonia | **LR** | Liberia | **SG** | Singapore | | |

# PSEUDO-PEPTIDE COMPOUNDS AS ANTAGONISTS OF NEUROKININES

## Technical field

The present invention refers to antagonists of the interaction between the P substance and the NK-1 receptor, the process for their preparation, and their use in pharmaceutical compositions which may be used in the treatment of pathological forms in which the P substance receptor is involved, and in particular in the treatment of the inflammation of airways, such as asthma and rhinitis, and in the treatment of emesis.

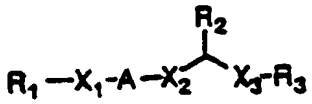
## State of the art

The problems deriving from the use of peptides having a high molecular weight as antagonist drugs of tachykinins have led to the search for the smallest peptide fragment still capable of exerting an antagonist action. These studies have resulted in the identification of tripeptides and dipeptides suitably derived, which are antagonists of the P substance (European patents EP 333174 and EP 394989).

Recently non-peptide antagonists have been identified, which thus do not present the drawbacks linked to the metabolic instability of peptides (patents WO 9413694, WO 9515311, and WO 9519966).

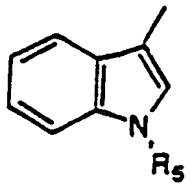
## Summary of the invention

In particular, the present invention regards compounds having the following general formula (I):



(I)

where $R_1$ is



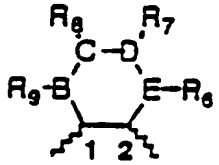
wherein $R_5$ is chosen from a group consisting of hydrogen or methyl,

$X_1$ is -CONH-

$X_2$ is $-NR_{12}CO-$, wherein $R_{12}$ is hydrogen or methyl;

$X_3$ is chosen in the group consisting of $-NR_{12}CO-$, $NR_{12}CONH-$, where $R_{12}$ is as defined above;

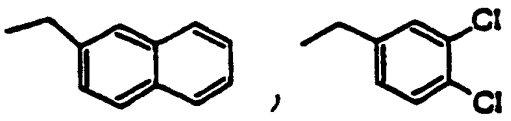
A is :




where B, C, D, and E, independently from each other, may be CH or N;

$R_6$, $R_7$, $R_8$ and $R_9$ are independently hydrogen, OH or $NR_{13}R_{14}$, where $R_{13}$ and $R_{14}$ are chosen independently in the group consisting of hydrogen, methyl, cyclohexyl, or 4-piperidine;

$R_2$ is chosen in the group consisting of




$R_3$ is chosen in the group consisting of aryl, aryl-alkyl radicals with a maximum of 15 carbon atoms, wherein the aryl group is chosen in the group consisting of benzene, naphtalene, benzofurane and indole and is possibly substituted on the ring with one or more substituents independently chosen in the group consisting of halogen, alkyl radical containing from 1 to 6 carbon atoms, possibly substituted with a number of fluorine atoms not higher than three (e.g., trifluoromethyl group), oxyalkyl radical containing from 1 to 6 carbon atoms, possibly substituted with a number of fluorine atoms not higher than three (e.g., trifluoromethoxyl group), tetrazole radical, $-NH_2$, $-NHR_{10}$, $-N(R_{10})_2$, $-OR_{10}$, $-CONHR_{10}$, $COR_{10}$, $COOR_{10}$, $R_{11}COOR_{10}$, $-OR_{11}COOR_{10}$, $-R_{11}COR_{10}$, $-CONHR_{10}$, $-R_{11}CONHR_{10}$, $-NHCOR_{10}$, and -nitro radicals, where $R_{10}$ is chosen in the group consisting of hydrogen or alkyl radical with linear or branched chain containing from 1 to 6 carbon atoms, and $R_{11}$ is an alkyldene radical with linear or branched chain containing from 1 to 6 carbon

atoms;

considering that:

- when one of the variables B, C, D, E is N, the others are CH.

Also forming part of the present invention are the corresponding pharmacologically acceptable salts and, in view of the presence of chiral centres, the possible optical isomers or mixtures of the same, also in racemic form.

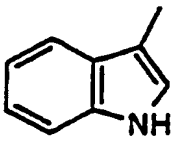
The compounds of formula (I), which have a receptor tachykinin antagonist activity, prove useful in the treatment of illnesses where tachykinins play a pathogenetic role, in particular arthritis, emesis, Huntington's disease, neuritis, neuralgia, hemicrania, hypertension, urinary incontinence, urticaria, signs indicating carcinoid syndrome, influenza and common cold, illnesses of the immune system, diseases of the respiratory tract (e.g., asthma, rhinitis of various forms and obstructive chronic bronchitis), ophthalmic illnesses (e.g., conjunctivitis), cutaneous illnesses (e.g., allergic and contact dermatitis and psoriasis), intestinal illnesses (e.g., ulcerative colitis and Chron's disease), tumors wherein the cells present a functionally espressed NK-1 receptor (in particular astrocytomas and gliomas).

**Detailed description of the invention**

It has been unexpectedly found, and this constitutes a fundamental characteristic of the present invention, that the compounds of formula (I), as previously defined, having non-peptide nature, present better characteristics of inhibition of the bond of tachykinins on the NK-1 receptor and a higher metabolic stability.

In particular, unexpectedly, if assayed in an *in vivo* test of inhibition of bronchospasm due to I.V. administration of agonist in guinea pigs, these compounds are active, both intravenously and orally, at doses of less than 1 nmole/kg, unlike the compounds claimed in patents WO 9515311 and WO 9519966, which, besides having a lower affinity for the NK-1 receptor, in the order of nanomoles, if assayed *in vivo* in the test described above, have an $ED_{50}$ of over 1 nmole/kg.

A preferred group of compounds of the present invention includes the compounds that may be described by the general formula (I), where

$R_1$ = 


where

$X_1$ = -CONH-, $X_2$ = -NHCO-, and $X_3$ = -$NCH_3$CO-;

$R_3$ = a benzyl group possibly substituted with one or more substituents chosen, independently from each other, in the group consisting of: Cl, Br, F, I, $CH_3$, $CF_3$, OH, $OCH_3$, $OCF_3$, $NH_2$, $NHCH_3$, $N(CH_3)_2$, COOH, $COOCH_3$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $NO_2$, CN;

and

$R_2$, $R_4$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{13}$, $R_{14}$, B, C, D, and E are as defined above.

Preferably, according to the present invention:

- the alkyl radical as defined for $R_3$ and $R_{10}$ and the alkyl-moiety of the oxyalkyl radical defined for $R_3$ are chosen in the group consisting of methyl, ethyl, propyl, and butyl;

- the aryl-alkyl radicals as defined for $R_3$ and the alkyliden-radicals as defined for $R_{11}$ present an alkylidene radical chosen in the group consisting of: methylene, ethylidene and propylidene;

and

- the halogen radical is chosen in the group consisting of chlorine, fluorine, bromine, and iodine.

In view of the centres of asymmetry present in formula (I), the invention refers to the various diastereoisomers included in the formula itself; in particular, the carbon atom bound to the substituent $R_2$ has R configuration.

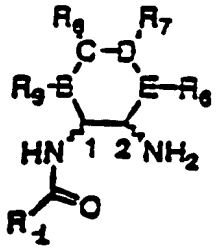
The compounds of the present invention have shown an antagonist activity of the action of the P substance, neurokinin A, and neurokinin B.

They can therefore be used as drugs in the treatment and prevention of illnesses where the tachykinins P substance, neurokinin A and neurokinin B are implicated as neuromodulators. Just to provide a few examples, the following illnesses may be mentioned: arthritis, emesis, Huntington's disease, neuritis, neuralgia, hemicrania, hypertension, urinary incontinence, urticaria, signs indicating carcinoid

syndrome, influenza and common cold, illnesses of the immune system, diseases of the respiratory tract (e.g., asthma, rhinitis of various forms and obstructive chronic bronchitis), ophthalmic illnesses (e.g., conjunctivitis), cutaneous illnesses (e.g., allergic and contact dermatitis and psoriasis), intestinal illnesses (e.g., ulcerative colitis and Chron's disease), tumors wherein the cells present a functionally espressed NK-1 receptor (in particular astrocytomas and gliomas).

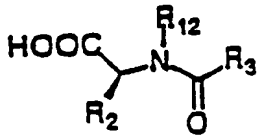
The compounds of general formula (I), as previously defined, are prepared according to the following reaction schemes and discussions, where, unless otherwise explicitly specified, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ and A are as previously defined.

a) By condensation of the intermediate compound of formula (IIa)



(IIa)

with the intermediate compound of formula (IIIa)



(IIIa)

the said intermediate of general formula IIa being prepared, for example, according to scheme 1, using a condensing agent that is well known to experts in the field or using, as species activated in the condensation reaction, an acyl halide.

The said intermediate of general formula IIIa is prepared, for example, according to scheme 2.

Scheme 2 describes the preparation of an intermediate of general formula IIIa, where $X_3$ = $NR_{12}CO$ and $R_2$ and $R_3$ are as defined previously, and the configuration of the carbon atom to which $R_3$ is bound is preferably R, the said intermediate being prepared by reaction between the derivative of the D-amino

acid of general formula (VI), available on the market or prepared by some other synthetic means obvious for experts in the field, and the acyl halide of general formula (VII), via prior silylation of the amino acid with *bis* (trimethylsilyl) acetamide. This acyl halide is prepared from the corresponding $R_3$-COOH carboxylic acid, following conventional methods that are obvious for experts in the field. The subsequent reaction is carried out in the presence of the alkyl halide of general formula $R_{12}$-Hal, where Hal is chosen from among a group comprising chlorine, iodine or bromine, and $R_{12}$ is as previously described, in the presence of a base, chosen in the group comprising alkaline or alkaline-earth hydrides, in an aprotic polar inert solvent, for example tetrahydrofuran or dioxane. Preferably the reaction is carried out at 0°C in tetrahydrofuran, using sodium hydride as a base and methyl iodide as alkylating agent.

The condensations described in the various schemes may be conveniently carried out according to any of the procedures described in the literature for the synthesis of peptides.

Excellent results, in terms of yield and purity of the products, have been obtained using, as condensing agent, benzotriazolyl tripyrrolidine phosphonio hexafluorophosphate (PyBop). In particular, the reaction was carried out adding PyBop slightly in excess to a solution of the carboxylic component, which was kept at a low temperature, followed by addition of the hydrochloride of the amine component and of a quantity of tertiary amine corresponding to three equivalents with respect to the condensing agent.

An alternative procedure involves the use, as condensing agent, of 1-ethyl-3-(3'-dimehtylaminopropyl)carbodiimide (WSC.HCl).

As regards the condensation reaction, which may be conveniently carried out at room temperature, conventional aprotic polar organic solvents are used, chosen in the group comprising dimethylformamide, dioxane, tetrahydrofuran, methylene chloride, dichloroethane, and chloroform.

A further characteristic of the present invention are therefore the processes of synthesis of the intermediates of general formulas (II) and (III), and the said intermediates that are obtained from the said processes.

The compounds of the present invention may exist in various isomeric forms. In

fact, whilst the configuration of the carbon linked to the substituent is uniquely prefixed by using during the synthesis the appropriate aminoacid derivative, the other starting products may consist of mixtures of stereoisomers that are difficult to separate. Consequently, the compounds of the present invention may be obtained as mixtures of diastereoisomers. The said mixtures may be resolved by chromatography. The compounds of formula (I) may in any case be used both in the optically active form and in the form of mixtures of isomers.

For therapeutical purposes, the compounds of the present invention may be administered through the parenteral intranasal, oral or sub-lingual routes. The formulations containing the new compounds may be prepared, according to known techniques, combining the active principle with an inert vehicle, and possibly with suitably chosen conventional additives. For oral or sub-lingual use, the compounds of the present invention may be administered in the form of tablets, capsules, drops, elixirs, etc., prepared using conventional vehicles/excipients, such as starch, sugars, water, alcohol, etc., and possibly containing flavouring agents, stabilizing agents, preserving agents, lubricants, etc. For parenteral or intranasal use, the vehicle of choice is sterile water for injections. Additives may be added according to the known art.

The therapeutically effective daily dosage will vary according to the subject to be treated (weight, age, degree of seriousness of the illness) and administration route. In general, however, the compounds of the invention are active when they are administered in a daily dosage of between 0.005 and 10 mg/kg. The pharmaceutical formulations of the present invention will thus contain the compounds of general formula (I) in quantities such as to guarantee an appropriate daily dosage within the range specified above, generally for administration from once to three times a day.

There follow a number of examples that are representative of the present invention, and the methods for their synthesis:

Example 1

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diamino-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl) alanyl)-

diaminocyclohexane

1a)Oxalyl chloride (512 µl) is added to a solution of 3-indolyl carboxylic acid (0.630 g) in 10 ml of $CH_2Cl_2$, and the solution is refluxed for 2 hours in nitrogen atmosphere. The solvent is eliminated by evaporation, and the solid is washed with hexane and dried under a stream of nitrogen to obtain crude acyl chloride (yield, 82%), which is passed on to the subsequent reaction without undergoing any further purification processes. A solution of the acyl chloride (0.530 g) in tetrahydrofuran (THF) is added, in nitrogen atmosphere in a period of 2 hours, to a solution of *cis* 1,2 diaminocyclohexane (1.15 ml) and diisopropylethylamine (DIEA) (0.61 ml) in 50 ml of THF. At the end of the addition, the solution is filtered, the filtrate is concentrated under reduced pressure, and the residue distributed between ethyl acetate (EtOAc) and HCl 1N in water. The aqueous phase is brought to pH 11 using NaOH and extracted with EtOAc. The organic extracts are re-united, washed with a saturated NaCl solution, de-hydrated on $Na_2SO_4$, and dried. The crude residue is triturated with $CH_3CN$, filtered and dried to yield 473 mg of *cis-N*-[(1(H)indol-3-yl-carbonyl)-1,2-diaminocyclohexane. TLC[chloroform/methanol/acetic acid 85/10/5 v/v (CMA)] $R_f$ = 0.12

For high-pressure liquid chromatography (HPLC), a column Phase Sep. Spherisorb ODS.2 5m 46 x 250 mm was used, and as eluents the following: A = 0.1 trifluoroacetic acid in acetonitrile; B = 0.1 trifluoroacetic acid in water; linear gradient from 20% of A to 80% of A in 25 min; isocratic 80% of A for 10 min; flow 1 ml/min; UV detection at 230 nm.

HPLC analysis revealed a single peak at $T_R$ = 14.44 min.

1b) Oxalyl chloride (462 µl) is added to a solution of *para*-tolylacetic acid (0.530 g) in 10 ml of $CH_2Cl_2$ (DCM), and the solution is refluxed for 1 hour in nitrogen atmosphere. The solvent and the excess oxalyl chloride are eliminated to obtain the crude acyl chloride (0.595 g), which is passed on to the subsequent reaction without undergoing any further purification processes. *Bis*(trimethylsilyl)acetamide (1.96 ml) is added to a suspension of D-3-(2-naphthyl)alanine (0.775 g) in 12 ml of THF. The suspension is kept stirred at room temperature until complete dissolution (approx. 1 hour), cooled down to 0°C, and a solution of the chloride of the *para*-tolylacetic acid (0.595 g) is added under stirring. The product is kept

stirred for 16 hours at room temperature. To this, 5 ml of water are added, and the solution is kept stirred for half an hour. The solvent is eliminated by evaporation under reduced pressure, and the residue is distributed between EtOAc and water. The organic phase is extracted with an aqueous solution and an NaCl saturated aqueous solution. The organic phase is dried. The crude product is crystallized using EtOAc to yield 0.953 g of N$^{\alpha}$ (4-methylphenylacetyl)-D-3(2-naphthyl)alanine.

TLC(CMA) $R_f$ = 0.60; $[a_D]$ = –65.1° (c 0.805, $CH_3OH$)

HPLC analysis revealed a single peak at $T_R$ = 20.24 min.

1c) Sodium hydride (58 mg, 80% in mineral oil) and iodomethane (0.306 ml) are added to a solution of the product of the previous step (0.213 g) in anhydrous THF (2 ml) kept at 0°C under stirring in a nitrogen atmosphere. The solution is kept stirred for 23 hours at room temperature. EtOAc is added, followed by 2 ml of water. The solvent is eliminated under reduced pressure, and the residue diluted in EtOAc and $NaHCO_3$ 5% aqueous solution. The aqueous phase is acidified to pH 2 using HCl 1N and extracted with EtOAc; the organic phase is washed with $H_2O$, aqueous $Na_2S_2O_3$, and finally with an NaCl saturated aqueous solution. The organic phase is filtered and dried. The crude product is purified by flash chromatography, eluting with acetic acid/toluene (27/63 v/v) to yield 0.181 g of N$^{\alpha}$ (4-methylphenylacetyl)-N$^{\alpha}$methyl-D-3(2-naphthyl)alanine.

TLC (20% acetic acid/toluene)$R_f$ = 0.23; $[a]_D$ = +54.7° (c 0.541, $CH_3OH$)

HPLC analysis revealed a single peak at $T_R$ = 22.66 min.

1d) 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSC.HCl) (0.285 g) is added in a single portion to a solution, cooled down to 0°C, of the product of step 1a (0.467 g), the product of the previous step 1c (0.438 mg), and 7-aza-1-hydroxybenzotriazole (HOAt) (0.202 g) in 15 ml of DCM. Collidine (0.437 ml) is added, and the solution is kept at room temperature for 24 hours. After the solvent has been eliminated under reduced pressure, the residue is diluted in ethyl acetate and extracted with a 5% solution of $NaHCO_3$, an aqueous solution of HCl 0.1N, and an NaCl saturated aqueous solution. The organic phase is dried. The two diastereoisomers are isolated by means of reverse-phase chromatography using a Hibar Merck column with 7-m Lichrosorb RP-18 filling, eluting with a gradient of from 32% water in methanol to 12% water in methanol

over a period of two hours, flow 8 ml/min. The fractions corresponding to the two isolated diastereoisomers are concentrated to a small volume under reduced pressure and lyophilized, yielding respectively 0.267 g and 0.254 g of the two diastereoisomers (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diamino-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane.

HPLC analysis, in the conditions of example 1a, revealed for each of the two products (defined as fast and slow according to whether they are eluted by the column before or after, respectively) a single peak: HPLC (fast) (Prog. 6) $T_R$ = 27.20 min. HPLC (slow) $T_R$ = 29.21 min.

Following a similar scheme of synthesis the following were prepared:

Example 2

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane

Example 3

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-chlorophenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-chlorophenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane

Example 4

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dimethyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dimethyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane

Example 5

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-trifluoromethyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-trifluoromethyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane

Example 6

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-bromo-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-bromo-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane

Example 7

(1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane and (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane

Example 8

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-trifluoromethyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-trifluoromethyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane

Example 9

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-bromo-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-bromo-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane

Example 10

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane

Example 11

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dimethyl-phenylacetyl)D-3(3,4-dichlorophenyl) alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dimethyl-phenylacetyl)D-3(3,4-dichlorophenyl) alanyl)-diaminocyclohexane

Example 12

(1R,2S)-1-*N*-[(1(H)indoi-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dichloro-phenylacetyl)D-3(3,4-dichlorophenyl) alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dichloro-phenylacetyl)D-3(3,4-dichlorophenyl) alanyl)-diaminocyclohexane

Example 13

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dichloro-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dichloro-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane

Example 14

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diamino-4-hydroxy-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diamino-4-hydroxy-cyclohexane

Example 15

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diamino-5-hydroxy-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diamino-5-hydroxy-cyclohexane

Example 16

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diamino-(4,5-dihydroxy)-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diamino-(4,5-dihydroxy)-cyclohexane

Example 17

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diamino-(4-hydroxy)-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diamino-(4-hydroxy)-cyclohexane

Example 18

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-

3(3,4-dichlorophenyl)alanyl)-diamino-5-hydroxy-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diamino-5-hydroxy-cyclohexane

Example 19

(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diamino-(4,5-dihydroxy)-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diamino-(4,5-dihydroxy)-cyclohexane

Example 20

(2R,3S)-2-*N*-[(1(H)indol-3-yl-carbonyl)-3-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminopiperidine and (2S,3R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminopiperidine

Example 21

(3R,4S)-3-*N*-[(1(H)indol-3-yl-carbonyl)-4-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminopiperidine and (3S,4R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminopiperidine

Example 22

(3R,4S)-3-*N*-[(1(H)indol-3-yl-carbonyl)-4-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminopiperidine and (3S,4R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminopiperidine

Example 23

(1R,2S)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-4-amino-diamino cyclohexane and (1S,2R)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-4-amino-diamino cyclohexane;

Example 24

(1R,2S)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-4-dimethylamino-diamino cyclohexane and (1S,2R)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-4-dimethylamino-diamino cyclohexane

Example 25

(1R,2S)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-diamino-5-amino cyclohexane and (1S,2R)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-5-amino -diamino cyclohexane

Example 26

(1R,2S)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-5-dimethylamino-diamino cyclohexane and (1S,2R)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-5-dimethylamino-diamino cyclohexane

Evaluation of the antagonist activity on NK-1 receptors was carried out with binding and functional *in vivo* assays and *in vivo* inhibition of bronchospasm induced by the agonist via intravenous administration.

The IM9-cell [H]SP binding assay was carried out as described in patents WO 95/15311 and WO 95/19965, and affinity was measured as pKi.

A functional assay in the isolated ileum of the guinea pig was carried out as described in patents WO 95/15311 and WO 95/19966, and the corresponding $pA_2$ values were calculated on the basis of the data thus obtained.

The antibronchospastic effect was evaluated using the method described by Perretti *et al.* in European Journal of Pharmacology, 273 (1995) 129-135.

[Sar$^{9}$, Met(O$_2$)$^{11}$] P substance is administered by intravenous route in doses of 1 nmol./kg at 15, 30 and 45 minutes before, and at 5, 30, 60, 90, 120, 150, and 180 minutes after IV administration of the vehicle or of the compounds to be tested (dose 0.08-1 μmol./kg).

Bronchoconstriction was evaluated in terms of increase in intra-pulmonary pressure.

The antagonist effect of the compound was determined as $ED_{50}$, expressed in μmol./kg, defined as the dose of antagonist necessary to decrease by 50% the bronchoconstrictive effect of the agonist for the entire duration of period of observation.

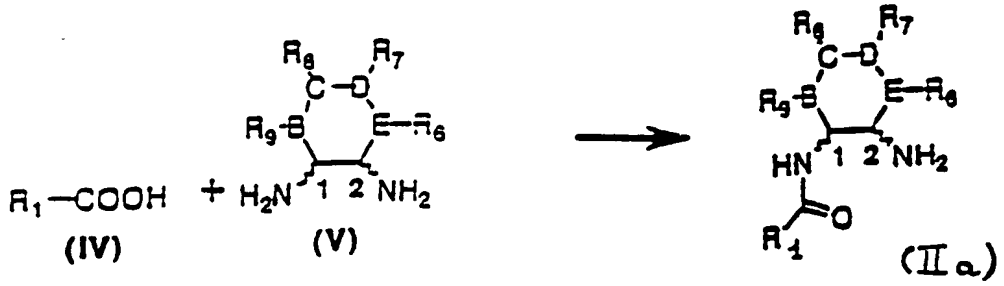
In the following TABLE the compound according to Example 1 was compared to the structurally closely related compounds described in Examples 3 and 11 of WO

95/15311.

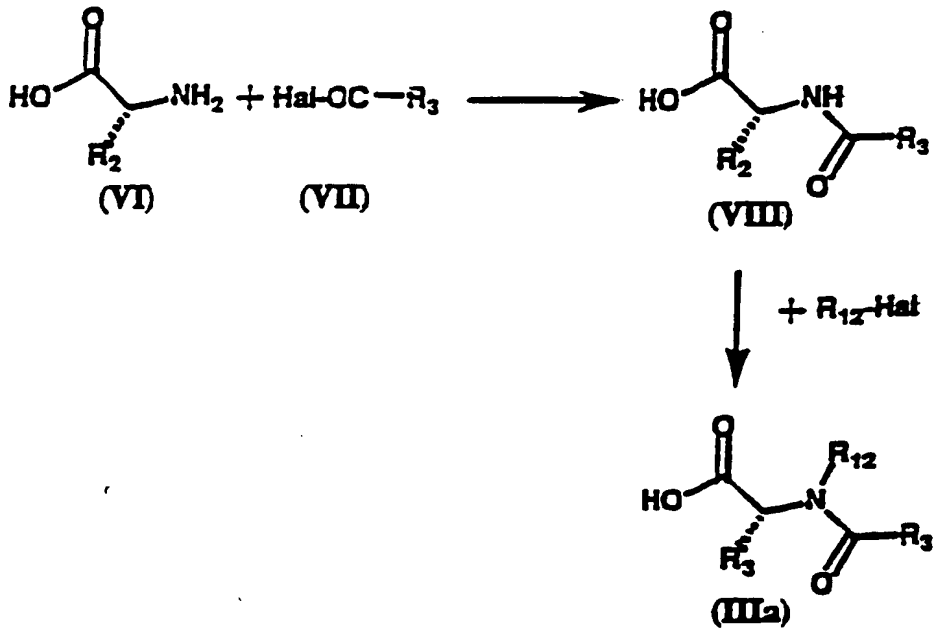
TABLE

| Compounds | pKi | pA2 | $ED_{50}$ |
|---|---|---|---|
| Ex. 1 | 9.6 | 10.3 | 0.04 |
| WO 95/15311 Ex. 3 | 8.4 | | 1.0 |
| WO 95/15311 Ex. 11 | 8.4 | | 0.069 |

SCHEME 1

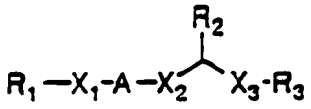



SCHEME 2



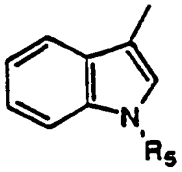
## CLAIMS

1. Compounds of general formula (I):



(I)

where $R_1$ is



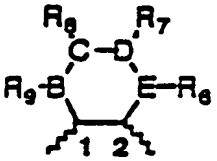
wherein $R_5$ is chosen from a group consisting of hydrogen or methyl,

$X_1$ is -CONH-

$X_2$ is $-NR_{12}CO-$, wherein $R_{12}$ is hydrogen or methyl;

$X_3$ is chosen in the group consisting of $-NR_{12}CO-$, $NR_{12}CONH-$, where $R_{12}$ is as defined above;

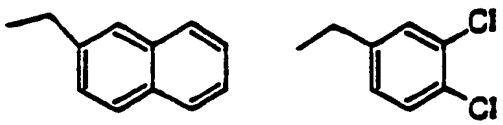
A is :



where B, C, D, and E, independently from each other, may be CH or N;

$R_6$, $R_7$, $R_8$ and $R_9$ are independently hydrogen, OH or $NR_{13}R_{14}$, where $R_{13}$ and $R_{14}$ are chosen independently in the group consisting of hydrogen, methyl, cyclohexyl, or 4-piperidine;

$R_2$ is chosen in the group consisting of



$R_3$ is chosen in the group consisting of aryl, aryl-alkyl radicals with a maximum of 15 carbon atoms, wherein the aryl group is chosen in the group consisting of benzene, naphtalene, benzofurane and indole and is possibly substituted on the ring with one or more substituents independently chosen in the group consisting of halogen, alkyl radical containing from 1 to 6 carbon atoms, possibly substituted with a number of fluorine atoms not higher than three (e.g., trifluoromethyl group), oxyalkyl radical containing from 1 to 6 carbon atoms, possibly substituted with a number of fluorine atoms not higher than three (e.g., trifluoromethoxyl group), tetrazole radical, $-NH_2$, $-NHR_{10}$, $-N(R_{10})_2$, $-OR_{10}$, $-CONHR_{10}$, $COR_{10}$, $COOR_{10}$, $R_{11}COOR_{10}$, $-OR_{11}COOR_{10}$, $-R_{11}COR_{10}$, $-CONHR_{10}$, $-R_{11}CONHR_{10}$, $-NHCOR_{10}$, and -nitro radicals, where $R_{10}$ is chosen in the group consisting of hydrogen or alkyl radical with linear or branched chain containing from 1 to 6 carbon atoms, and $R_{11}$ is an alkyldene radical with linear or branched chain containing from 1 to 6 carbon atoms;

considering that:

- when one of the variables B, C, D, E is N, the others are CH.

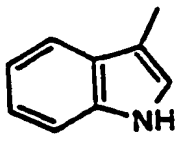
2. Compound according to Claim 1 wherein

- the alkyl radical as defined for $R_3$ and $R_{10}$ and the alkyl-moiety of the oxyalkyl radical defined for $R_3$ are chosen in the group consisting of methyl, ethyl, propyl, and butyl;
- the aryl-alkyl radicals as defined for $R_3$ and the alkyliden-radicals al defined for $R_{11}$ present an alkylidene radical chosen in the group consisting of: methylene, ethylidene and propylidene;

and

- the halogen radical is chosen from among chlorine, fluorine, bromine, and iodine.

3. Compound according to Claim 1, where

$R_1$ = 


$X_1$ = -CONH-, $X_2$ = -NHCO-, $X_3$ = $-NCH_3CO-$;

$R_3$ is a benzyl group possibly substituted with one or more substituents chosen, independently from each other, in the group consisting of: Cl, Br, F, I, $CH_3$, $CF_3$, OH, $OCH_3$, $OCF_3$, $NH_2$, $NHCH_3$, $N(CH_3)_2$, COOH, $COOCH_3$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $NO_2$, CN;

$R_2$, $R_4$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{13}$, $R_{14}$, B, C, D, and E are as defined in claim 1, and where the carbon atom bound to the substituent $R_2$ has an R configuration.

4. Compounds of general formula (I), according to Claims from 1 to 3, as specified below:

1) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diamino-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl) alanyl)-diaminocyclohexane

2) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane

3) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-chlorophenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-chlorophenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane

4) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dimethyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dimethyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane

5)(1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-trifluoromethyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-trifluoromethyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane

6) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-bromo-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-bromo-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane

7) (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane and (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane

8) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-trifluoromethyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-trifluoromethyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane

9) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-bromo-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-bromo-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane

10) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminocyclohexane

11) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dimethyl-phenylacetyl)D-3(3,4-dichlorophenyl) alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dimethyl-phenylacetyl)D-3(3,4-dichlorophenyl) alanyl)-diaminocyclohexane

12) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dichloro-phenylacetyl)D-3(3,4-dichlorophenyl) alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dichloro-phenylacetyl)D-3(3,4-dichlorophenyl) alanyl)-diaminocyclohexane

13) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dichloro-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(3,4-dichloro-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminocyclohexane

14) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diamino-4-hydroxy-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-

naphthyl)alanyl)-diamino-4-hydroxy-cyclohexane

15) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diamino-5-hydroxy-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diamino-5-hydroxy-cyclohexane

16) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diamino-(4,5-dihydroxy)-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diamino-(4,5-dihydroxy)-cyclohexane

17) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diamino-(4-hydroxy)-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diamino-(4-hydroxy)-cyclohexane

18) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diamino-5-hydroxy-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diamino-5-hydroxy-cyclohexane

19) (1R,2S)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diamino-(4,5-dihydroxy)-cyclohexane and (1S,2R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diamino-(4,5-dihydroxy)-cyclohexane

20) (2R,3S)-2-*N*-[(1(H)indol-3-yl-carbonyl)-3-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminopiperidine and (2S,3R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminopiperidine

21) (3R,4S)-3-*N*-[(1(H)indol-3-yl-carbonyl)-4-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminopiperidine and (3S,4R)-1-*N*-[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(2-naphthyl)alanyl)-diaminopiperidine

22) (3R,4S)-3-*N*-[(1(H)indol-3-yl-carbonyl)-4-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminopiperidine and (3S,4R)-1-*N*-

[(1(H)indol-3-yl-carbonyl)-2-*N*(N$^{\alpha}$methyl-N$^{\alpha}$(4-methyl-phenylacetyl)D-3(3,4-dichlorophenyl)alanyl)-diaminopiperidine

23) (1R,2S)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-diamino-4-amino cyclohexane and (1S,2R)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-diamino-4-amino cyclohexane;

24) (1R,2S)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-diamino-4-dimethylamino cyclohexane and (1S,2R)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-diamino-4-dimethylamino cyclohexane

25) (1R,2S)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-diamino-5-amino cyclohexane and (1S,2R)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-diamino-5-amino cyclohexane

26) (1R,2S)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-diamino-5-dimethylamino cyclohexane and (1S,2R)-1-N-[(1(H)indol-3-yl-carbonyl)-2-N(N$^{\alpha}$methyl-N$^{\alpha}$4-methyl-phenylacetyl)D-3(2-naphtyl)alanyl)-diamino-5-dimethylamino cyclohexane

5. Pharmaceutical composition comprising as active principle an effective dose of the compounds of formula (I), as specified in Claim 1, for use as antagonists of tachykinins.

6. Pharmaceutical composition comprising as active principle an effective dose of the compounds specified in Claim 2, for use as antagonists of tachykinins.

7. Pharmaceutical composition comprising as active principle an effective dose of the compounds specified in Claim 3, for use as antagonists of tachykinins.

8. Pharmaceutical composition comprising as active principle an effective dose of the compounds specified in Claims 1, 2, 3 and 4, for use as antagonists of tachykinins, and in particular in the treatment of arthritis, emesis, Huntington's disease, neuritis, neuralgia, hemicrania, hypertension, urinary incontinence, urticaria, signs indicating carcinoid syndrome, influenza and common cold, illnesses of the immune system, ophthalmic illnesses (e.g., conjunctivitis), cutaneous illnesses (e.g., allergic and contact dermatitis and psoriasis), intestinal

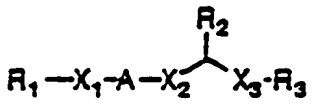
illnesses (e.g., ulcerative colitis and Chron's disease), tumors wherein the cells present a functionally espressed NK-1 receptor (e.g. astrocytomas and gliomas).

9. Pharmaceutical compositions comprising as active principle an effective dose of a compound according to Claims 1 - 4 for use as antagonists of tachykinins in the treatment of diseases of the respiratory tract such as asthma, rhinitis of various forms and obstructive chronic bronchitis and inflamation of the upper air tract.

10. Use of the compounds of formula (1), as specified in Claims 1, 2, 3, and 4, as active principles for the preparation of pharmaceutical compositions to be used as antagonists of tachykinins, and in particular in the treatment of arthritis, emesis, Huntington's disease, neuritis, neuralgia, hemicrania, hypertension, urinary incontinence, urticaria, signs indicating carcinoid syndrome, influenza and common cold, illnesses of the immune system, ophthalmic illnesses (e.g., conjunctivitis), cutaneous illnesses (e.g., allergic and contact dermatitis and psoriasis), intestinal illnesses (e.g., ulcerative colitis and Chron's disease), tumors wherein the cells present a functionally espressed NK-1 receptor (e.g. astrocytomas and gliomas).

11. Use of the compounds of formula (1), as specified in Claims 1, 2, 3, and 4, as active principles for the preparation of pharmaceutical compositions to be used as antagonists of tachykinins in the treatment of diseases of the respiratory tract such as asthma, rhinitis of various forms and obstructive chronic bronchitis and inflamation of the upper air tract.

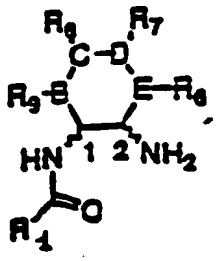
12. Process for the preparation of an NK-1 antagonist of general formula (I)



(I)

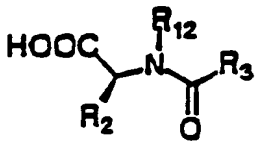
where the various substituents are as defined in Claim 1; the said process being characterized by the following steps of synthesis:

a) synthesis of the intermediate compound of synthesis of formula (IIa)



(IIa)

and of the intermediate compound of formula (IIIa)



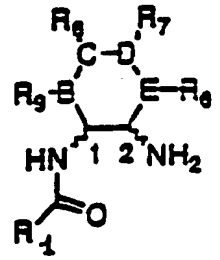
(IIIa)

where, unless otherwise explicitly specified, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, and $R_{12}$ are as defined above;

b) condensation, in the presence of a suitable condensing agent, of the two appropriate intermediate compounds;

c) isolation and purification of the product of step b) by chromatography.

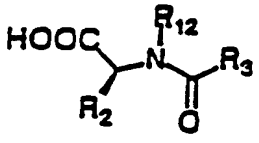
13. Compound of general formula (IIa)



(IIa)

where $R_2$, $R_6$, $R_7$, $R_8$, $R_9$, A, B, C, and D are as specified in Claim 1.

14. Compound of general formula (IIIa)



(IIIa)

where $R_2$, $R_3$, and $R_{12}$ are as claimed in Claim 1.

# INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 98/02010

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/42 A61K31/40 C07D401/12

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 94 13694 A (A. MENARINI INDUSTRIE FARMACEUTICHE RIUNITE S.R.L.) 23 June 1994 cited in the application see claims | 1,5 |
| A | WO 95 15311 A (A. MENARINI INDUSTRIE FARMACEUTICHE RIUNITE S.R.L.) 8 June 1995 cited in the application see claims | 1,5 |
| X | see page 16, line 4-5 - line 19-20 | 14 |
| A | WO 95 19966 A (A. MENARINI INDUSTRIE FARMACEUTICHE RIUNITE S.R.L.) 27 July 1995 cited in the application see claims | 1,5 |

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of theinternational search | Date of mailing of the international search report |
|---|---|
| 2 September 1998 | 24/09/1998 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Van Bijlen, H |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/02010

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | STEFAN TAUDIEN ET AL: "Unusual amino acids III. Asymmetric synthesis of 3-arylalanines" TETRAHEDRON: ASYMMETRY., vol. 4, no. 1, - 1993 pages 73-84, XP002076304 OXFORD GB * page 76,81: compounds 31(R)(S) * --- | 14 |
| X | APRYLL M. STALCUP ET AL: "Effect of the configuration of the substituents of derivatized beta-cyclodextrin bonded phases on enantioselectivity in normal-phase liquid chromatography " JOURNAL OF CHROMATOGRAPHY, vol. 540, - 1991 pages 113-128, XP002076305 see page 119 --- | 14 |
| X | WO 95 12611 A (CIBA-GEIGY JAPAN LTD.) 11 May 1995 * example 50, starting compound * ----- | 14 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
PCT/EP 98/02010

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9413694 A | 23-06-1994 | IT 1256623 B | 12-12-1995 |
| | | AU 5650894 A | 04-07-1994 |
| | | CA 2151062 A | 23-06-1994 |
| | | DE 69312319 D | 21-08-1997 |
| | | DE 69312319 T | 08-01-1998 |
| | | EP 0672052 A | 20-09-1995 |
| | | ES 2105605 T | 16-10-1997 |
| | | US 5641802 A | 24-06-1997 |
| WO 9515311 A | 08-06-1995 | IT FI930247 A | 05-06-1995 |
| | | AU 1273195 A | 19-06-1995 |
| | | CA 2177994 A | 08-06-1995 |
| | | EP 0731790 A | 18-09-1996 |
| | | JP 9506348 T | 24-06-1997 |
| | | US 5760248 A | 02-06-1998 |
| WO 9519966 A | 27-07-1995 | IT FI940009 A | 19-07-1995 |
| | | AU 1574995 A | 08-08-1995 |
| | | CA 2181451 A | 27-07-1995 |
| | | EP 0740656 A | 06-11-1996 |
| | | US 5698710 A | 16-12-1997 |
| WO 9512611 A | 11-05-1995 | AU 691201 B | 14-05-1998 |
| | | AU 7856594 A | 23-05-1995 |
| | | BR 9407933 A | 26-11-1996 |
| | | CA 2173875 A | 11-05-1995 |
| | | EP 0728145 A | 28-08-1996 |
| | | FI 961804 A | 30-04-1996 |
| | | NO 961725 A | 29-04-1996 |
| | | US 5780498 A | 14-07-1998 |
| | | ZA 9408541 A | 02-05-1995 |